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ORIGINAL ARTICLE

Safety and efficacy of intraoperative radiation therapy using a low-energy X-ray source for resectable pancreatic cancer: an interim evaluation of an ongoing prospective phase II study

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ABSTRACT

Objective: The role of intraoperative radiation therapy (IORT) in the management of resectable pancreatic cancer (RPC) remains unclear. To date, the application of IORT using a low-energy X-ray source has not been extensively investigated. Therefore, this study was conducted to evaluate the safety and efficacy of IORT using a 50 kV X-ray source in treating RPC.

Methods: Patients with RPC who underwent radical pancreatectomy and IORT were enrolled. The primary endpoint was time to treatment failure (TTF) survival, whereas the secondary endpoints were safety and overall survival (OS).

Results: By November 2023, 35 patients with RPC were treated according to the study protocol. The median TTF was 11.67 months, whereas the median OS for the cohort was 22.2 months. The local recurrence rate was 20%. The most common postoperative complication was pancreatic fistula. The incidence of delayed gastric emptying was 20%. Within 30 days after surgery, one patient experienced abdominal pain, another experienced vomiting, and one died because of abdominal infection and a grade C pancreatic fistula. Carcinoembryonic antigen (CEA) and D-dimer levels significantly correlated with TTF and OS in multivariate analyses. The carbohydrate antigen 19-9 (CA19-9) level was another prognostic factor significantly associated with OS. Patients with low D-dimer and normal CA19-9 levels showed prolonged OS with an IORT dose ≤ 15 Gy.

Conclusions: This study supports use of IORT with a 50 kV X-ray source in treating RPC. IORT using a low-energy X-ray source was well-tolerated and feasible. Additionally, D-dimer, CEA, and CA19-9 levels may help identify patient profiles potentially benefitting from IORT.

KEYWORDS Resectable pancreatic cancer; intraoperative radiation; survival; complications; benefit group

Introduction

Pancreatic cancer is associated with poor clinical outcomes and has a 5-year survival rate below 13%[1]. Surgical resection remains the primary treatment modality; however, only 15%–20% of patients are eligible for radical surgery at diagnosis[2]. Even with adjuvant chemotherapy, the overall prognosis remains suboptimal[3]. Local failure rates are as high as 50%–80% in patients with resected and locally advanced disease[4]. One report has indicated that 30% of all patients with pancreatic cancer die from locally destructive disease[5]. Achieving higher local control rates is crucial for improving patient prognosis and quality of life.

Intraoperative radiation therapy (IORT) involves delivery of a single high-dose fraction of radiation during surgery[6]. The target volume typically includes the tumor bed after gross total resection or any residual disease if complete resection is not feasible. IORT is more frequently used for locally advanced pancreatic cancer[7,8] but has also shown effectiveness

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in treating resectable pancreatic cancer[9-13]. IORT has been shown to achieve 40%–80% lower locoregional recurrence than observed with standard treatment[14]. A meta-analysis has revealed that IORT improves locoregional control and overall survival (OS) in patients with resectable pancreatic cancer without increasing postoperative complications or surgery-associated mortality rates[15]. However, some researchers contend that the benefits of IORT are limited to carefully selected patients with non-metastatic disease[8,16,17]. Despite its potential, experience with IORT in resectable pancreatic cancer remains limited, and the effects of treatment on time to failure (TTF) survival and OS are unclear.

The 2 primary approaches for IORT in pancreatic cancer are electron beams and high-dose-rate brachytherapy[18]. IORT using electron beams poses safety concerns because patients must be transferred from the operating room to a shielded radiation room. In contrast, the miniaturized low-energy X-ray source used in INTRABEAM allows IORT to be administered directly in the operating room. However, no clear evidence is available regarding the safety of IORT using 50 kV X-rays, and the optimal radiation dose has not been established.

Delivering high-dose-rate brachytherapy to the pancreas is particularly challenging, because of the proximity of several radiosensitive abdominal organs. However, image-guided IORT and online treatment planning significantly improve the accuracy of these procedures[19]. Consequently, image-guided IORT plays a crucial role in the treatment of pancreatic cancer.

In a recent study, IORT was administered with a mobile 50kV X-ray source (Intrabeam 600, Carl Zeiss, Germany). Image-guided IORT was facilitated by intraoperative cone beam computed tomography (CBCT). The primary objective of the present study was to evaluate the local control, long-term survival, safety, and feasibility of IORT in patients with pancreatic cancer undergoing surgical resection. Additionally, this study was aimed at investigating the correlation between patient characteristics and survival outcomes, and identifying effective methods for determining which patients might benefit from IORT.

Materials and methods

Study population and clinical data

The records of patients with pancreatic cancer treated with IORT with a 50 kV X-ray source and undergoing distal pancreatectomy with en bloc splenectomy were reviewed. The purpose of this clinical trial was to evaluate the efficacy and safety of IORT using a low-energy X-ray source. Patients were stratified by IORT dose (≤ 15 Gy *vs.* > 15 Gy). At our institution, patients with pancreatic cancer underwent distal pancreatectomy, and an IORT dose of 15 Gy with a 50 kV X-ray source is our routine clinical practice. Therefore, we chose 15 Gy as the cut-off for stratification. The Institutional Review Board of Tianjin Medical University Cancer Institute & Hospital approved the study (protocol number: E20230004). Written informed consent was obtained from all participants.

Patients who were diagnosed with pancreatic cancer at Tianjin Medical University Cancer Institute & Hospital between February 2021 and November 2023, and who provided informed consent, were enrolled in this study. Data were collected from blood tests performed 1 week before surgery and before the initiation of adjuvant chemotherapy.

Key eligibility criteria included the following: (1) age ≥ 18 years; (2) resectable or borderline resectable pancreatic cancer, as defined by National Comprehensive Cancer Network guidelines[20], and confirmed *via* CT, endoscopic ultrasound, or other imaging modalities; (3) good Eastern Cooperative Oncology Group performance status (0–1); (4) tumor location in the pancreatic body or tail, making distal pancreatectomy with en bloc splenectomy technically feasible; (5) candidacy for IORT; (6) sufficient organ function to tolerate surgery and IORT.

Key exclusion criteria included the following: (1) presence of severe comorbidities, such as heart failure, renal failure, liver failure, bleeding peptic ulcer, intestinal paralysis, intestinal obstruction, or uncontrolled diabetes; (2) tumors located in the pancreatic head or neck; (3) evidence of disease not localized to the pancreas; (4) current enrolment in another investigational drug or device trial clinically interfering with this study; (5) inability to comply with the study requirements or follow-up schedule; (6) women with childbearing potential or sexually active fertile men whose partners were women of childbearing potential who were unwilling or unable to use acceptable contraception methods throughout the study; (7) history of active cancer, including concurrent multiple cancers or heterogeneous multiple cancers with a disease-free interval < 3 years.

After the resection phase, intraoperative radiotherapy images were collected and reconstructed in 3 dimensions with CBCT (Cios Spin 3D, Siemens Healthineers, Germany). The three-dimensional (3D) images were then imported into specialized planning software for intraoperative radiotherapy (PUNENG IORT treatment planning system, China) to

accurately calculate and evaluate the target radiation dose. A mobile 50kV X-ray source was used for IORT. The target volume included the tumor bed, the celiac and superior mesenteric arteries, the mesenteric root, and any additional areas considered to be at risk by the surgeon and radiation oncologist. The radiation dose guidelines recommended 10–20 Gy to the resection bed[21]. Age, physical condition, site of irradiation, and dose limiting factors of the organ at risk were factors influencing dose selection. The current INTRABEAM treatment planning model uses a method for calculating delivered doses according to the 1-dimensional fit of a look-up table of depth dose rates measured in water along the central axis of the X-ray source. On the basis of the dose rate and the penetration depth, the INTRABEAM 600 calculates the total exposure time. Patients received adjuvant chemotherapy 4–12 weeks after surgery.

Follow-up and toxicity evaluation

All patients were followed up according to the institutional protocol, which comprised evaluations every 3 months for the first 2 years after treatment, followed by evaluations every 6 months for an additional 3 years. Routine restaging occurred every 6 months with a computed tomography (CT) scan of the abdomen and pelvis. Carbohydrate antigen 19-9 (CA 19-9) levels were measured, and follow-up CT scans (chest, abdomen, and pelvis) with contrast were performed every 3–6 months for the first 2 years after surgical resection. Surgical complications were assessed with the Clavien–Dindo classification.

Statistical analysis

Statistical analysis was conducted in SPSS (version 19.0) statistical software. The primary endpoint was TTF survival, whereas secondary endpoints included safety and OS. TTF was defined as the interval from surgery to the first radiologic evidence of recurrent disease at any site or to the date of the last imagiological examination if no disease recurrence was observed. OS was measured from the time of surgery to the patient's death, regardless of cause, or to the date of censoring. The Kaplan-Meier method was used to estimate the probability of TTF and OS. Potential associations were evaluated through univariate and multivariate analyses with the Cox proportional hazards model with a significance threshold of $P < 0.05$ (two-tailed). The relationships between treatment and clinicopathologic parameters were assessed with the χ^2 test or Fisher's exact test. Receiver operating characteristic curves were calculated, and the Youden index was estimated to determine the optimal cut-off value for factors without reference values. The cut-off values for D-dimer, CEA, and CA19-9 were at the upper limit of normal in our hospital.

Results

From February 2021 to November 2023, 37 patients with RPC were enrolled. Two patients were excluded from the analysis because of intraoperative findings of distant metastasis. The last follow-up occurred on November 4, 2024. A total of 31 patients completed at least 1 year of follow-up. The number of patients followed up for more than 2 years was 15 (42.9%). The median follow-up duration for the entire patient cohort was 23.2 months (range: 2.8–44.3 months). Two patients were lost to follow-up, and 13 patients were alive at the time of analysis. **Table 1** displays the patient and disease characteristics.

The median age of all patients was 67 years (range: 52–76 years). All participants underwent R0 resection. An applicator with an appropriate diameter (2.0, 3.0, 4.0, or 5.0 cm) was selected according to the size of the target volume and was attached over the probe of the X-ray source. The median applicator diameter was 3.0 cm. Four patients did not undergo adjuvant chemotherapy: 2 declined chemotherapy, 1 was lost to follow-up, and another died in the hospital because of abdominal infection and grade C pancreatic fistula. At present, only 2 stage III patients have been recruited; therefore, no subgroup analysis was performed for staging. The predefined subgroups of patients according to IORT dose showed no significant differences in TTF and OS. All variables listed in **Table 1** were included in the univariate analyses.

TTF survival

Of the 35 patients analyzed, 7 experienced local recurrence, thus resulting in a locoregional recurrence rate of 20%; 23 had distant metastases; and 5 showed both local recurrence and distant metastases. The median time to local failure was 9.8 months (range: 1.1–38.1 months). The median TTF was 11.67 months (range: 1.1–40.0 months). The median TTF was 11.667 months in the IORT dose ≤ 15 Gy group ($n = 28$) and 7.6 months in the IORT dose > 15 Gy group ($n = 7$, $P = 0.53$). The median TTF for stages I ($n = 9$), II ($n = 24$), and III ($n = 2$) was 20.867 months, 9.2 months and 2.1 months, respectively ($P = 0.216$).

Table 1 Patient and disease characteristics

	No. of patients	Percentage
Age (mean 67 years)		
< 67	17	48.6
≥ 67	18	51.4
Gender		
Female	18	51.4
Male	17	48.6
Symptom		
Yes	30	85.7
No	5	14.3
Weight loss		
Yes	15	42.9
No	20	57.1
Neoadjuvant chemotherapy		
Yes	11	31.4
No	24	68.6
Type of surgery		
DP	14	40
DP + adrenalectomy	12	34.3
DP + other	9	25.7
T		
T1	1	2.9
T2	18	51.4
T3	16	45.7
N		
N0	18	51.4
N1	15	42.9
N2	2	5.7
Perineural invasion		
Yes	26	74.3
No	9	25.7
AJCC stage		
I	9	25.7
II	24	68.6
III	2	5.7
IORT dose (Gy)		
12	1	2.9
15	27	77.1
20	7	20.0
Applicator diameter (cm)		
2	4	11.5
3	16	45.7
4	13	37.1
5	2	5.7
Pre-operative CA19-9 (U/mL)		
< 37	15	42.9
≥ 37	20	57.1
Pre-operative CEA (ng/mL)		
< 5	24	68.6
≥ 5	11	31.4
D-dimer (ng/mL)		
< 500	10	28.6
≥ 500	25	71.4
Adjuvant chemotherapy		
Yes	31	88.6
No	4	11.4
Adjuvant chemotherapy		
Gemcitabine	3	8.6
S1	5	14.3
Gemcitabine + S1	8	22.9
Gemcitabine + albumin-bound paclitaxel	9	25.7
Albumin-bound paclitaxel + S1	2	5.7
FOLFIRINOX	4	11.4

DP, distal pancreatectomy; AJCC, American Joint Committee on Cancer; IORT, intraoperative radiation therapy; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; S1, tegafur, gimeracil and oteracil potassium capsules; FOLFIRINOX, fluorouracil + leucovorin + irinotecan + oxaliplatin.

Univariate analyses revealed a significantly elevated risk of recurrence among patients with elevated preoperative CEA ($P = 0.036$) (**Figure 1A**) and D-dimer ($P = 0.005$) levels (**Table 2** and **Figure 1B**). Among the 24 patients in the CEA < 5 ng/mL group, CT evaluations revealed local recurrence and/or distant metastasis in 14 patients. Nine recurrences and/or distant metastases occurred among the 11 patients with CEA ≥ 5 ng/mL. Only 1 patient (10%) had local recurrence in the D-dimer < 500 ng/mL group ($n = 10$). The other 6 (24%) local

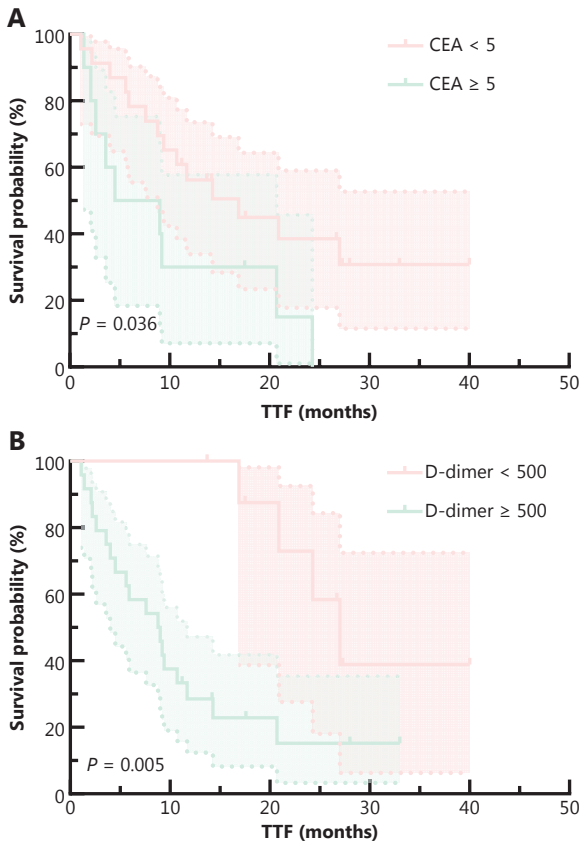

Figure 1 Kaplan-Meier survival curves showing time to failure (TTF) survival according to CEA (A) D-dimer (B).

recurrent events occurred in the 25 participants with high D-dimer levels. CEA and D-dimer levels significantly correlated with TTF in multivariate analyses (**Table 3**).

Age, gender, receipt of neoadjuvant and adjuvant treatment, surgery type, TNM stage, chemotherapy regimens, IORT dose, and CA19-9 were not significantly associated with TTF. Patients with normal serum CEA levels had a significantly longer median TTF than those with elevated CEA levels (16.90 *vs.* 6.75 months). The median TTF was 27.0 months in the D-dimer < 500 ng/mL group and 8.9 months in the high D-dimer group.

Subgroup analysis

In the group with IORT dose ≤ 15 Gy, only D-dimer level was associated with TTF. Patients with D-dimer < 500 ng/mL had a significantly longer median TTF than those with D-dimer ≥ 500 ng/mL (26.967 months *vs.* 8.967 months, 95% CI 8.066-9.868, $P = 0.001$). No significant prognostic factors were identified in the IORT dose > 15 Gy group.

OS

Among the 20 deceased patients, 18 (90%) died because of cancer progression, whereas 1 (5%) died because of treatment-associated toxicity, and another (5%) died because of SARS-CoV-2 infection. The median OS time for the entire cohort was 22.2 months. The median OS was 21.7 months in the IORT dose ≤ 15 Gy group and 22.2 months in the IORT dose > 15 Gy group ($P = 0.984$).

Univariate analyses indicated that stage II/III, and higher D-dimer levels and preoperative CEA and CA19-9 levels were associated with poorer OS (**Table 2** and **Figure 2**). Furthermore, multivariate analysis revealed that D-dimer levels and preoperative CEA and CA19-9 levels were independent prognostic factors for OS (**Table 3**).

The mortality rates in the low and high D-dimer groups were 30% (3/10) and 68% (17/25), respectively. Moreover, 11 of 24 patients with CEA < 5 ng/mL died. Of the 11 patients in the CEA < 5 ng/mL group, 9 died, whereas 6 of 15 patients died in the CA19-9 < 37 U/mL group. In the other 20 patients with CA19-9 ≥ 37 U/mL, the number of death events was 14. The median OS was not reached in the D-dimer < 500 ng/mL group and was 15.067 months in the high D-dimer group.

Table 2 Univariate analysis of associations of patient, tumor, treatment, and pathologic characteristics with survival

Variable	Time to failure survival		Overall survival	
	95% CI	*P* value	95% CI	*P* value
TNM stage	4.906–18.427	0.216	7.128–41.206	0.007*
IORT dose ≤ 15 (*vs.* > 15)	2.382–12.818	0.530	0.001–56.159	0.984
D-dimer < 500 (*vs.* ≥ 500)	4.906–18.427	0.005*	10.267–38.067	0.016*
CEA < 5 (*vs.* ≥ 5)	4.906–18.427	0.036*	7.790–20.610	0.002*
CA19-9 < 37 (*vs.* ≥ 37)	0.715–16.219	0.112	10.520–18.946	0.001*

*$P < 0.05$ was considered statistically significant. CI, confidence interval.

Table 3 Multivariate analysis of associations of patient, tumor, treatment, and pathologic characteristics with survival

Variable	Time to failure survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
TNM stage	1.393	0.59–3.289	0.449	0.125	0.006–2.384	0.350
IORT dose ≤ 15 (*vs.* > 15)	0.389	0.139–2.157	0.547	2.120	0.473–9.509	0.326
D-dimer < 500 (*vs.* ≥ 500)	0.219	0.070–0.682	0.009*	0.230	0.070–0.763	0.016*
CEA < 5 (*vs.* ≥ 5)	0.384	0.159–0.928	0.034*	0.281	0.109–0.725	0.009*
CA19-9 < 37 (*vs.* ≥ 37)	0.666	0.282–1.569	0.352	0.234	0.079–0.692	0.009*

*P < 0.05 was considered statistically significant. HR, hazard ratio; CI, confidence interval.

Patients with normal serum CEA levels had a significantly longer median OS than those with abnormal CEA levels (29.8 *vs.* 11.9 months). The median OS was not reached in the CA19-9 < 37 U/mL group and was 14.733 months in the CA19-9 ≥ 37 U/mL group.

Subgroup analysis

In the group receiving an IORT dose ≤ 15 Gy, univariate analyses revealed a significantly greater risk of death among patients with elevated D-dimer (P = 0.026), CA19-9 (P = 0.005), and CEA (P = 0.033) levels. In the multivariate analysis, D-dimer (HR, 0.153; 95% CI 0.036–0.655, P = 0.011) and CA19-9 (HR, 0.164; 95% CI 0.042–0.637, P = 0.009) levels were independently associated with OS. The median OS was not reached in the D-dimer < 500 ng/mL group and was 15.067 months in the D-dimer ≥ 500 ng/mL group. Patients with normal CA19-9 levels had a significantly longer median OS than those with abnormal levels (not reached *vs.* 14.733 months). Patients with low D-dimer and normal CA19-9 levels showed prolonged OS. No significant prognostic factors were identified in the group receiving an IORT dose > 15 Gy group.

Postoperative complications

Pancreatic fistula was the most common complication (n = 33, 94.2%), among which 30 cases were classified as grade A. A total of 27 patients (81.8%) in the IORT dose ≤ 15 Gy group and 6 patients (18.2%) in the IORT dose > 15 Gy group experienced pancreatic fistula (P = 0.365). Two patients receiving 12 Gy experienced grade B pancreatic fistula. The 1 patient with a grade C pancreatic fistula received a dose of IORT of 20 Gy. Other postoperative complications included delayed gastric emptying and intra-abdominal abscess (**Table 4**). A total of 6 of 28 patients experienced delayed gastric emptying in the group receiving an IORT dose ≤ 15 Gy. The number of delayed gastric emptying events was 1 among the other 7 patients receiving an IORT dose > 15 Gy. Most of these complications were managed conservatively. However, one patient who received a 20 Gy dose died in the hospital, because of multiple organ failure, abdominal infection, and a grade C pancreatic fistula. The average length of hospital stay was 18.69 days. Additionally, one patient was readmitted with abdominal pain, and another experienced delayed gastric emptying within 30 days after surgery (**Table 4**).

Discussion

This study assessed the efficacy and safety of intraoperative radiation therapy in 35 patients with pancreatic cancer who underwent radical distal pancreatectomy with en bloc splenectomy. Regarding treatment efficacy, the median TTF was 11.67 months, and the OS for the entire cohort was 22.2 months. The locoregional recurrence rate was 20%. Most postoperative complications were manageable.

Pancreatic cancer remains among the most challenging malignancies to treat, despite advancements in surgery, chemotherapy, and radiation therapy, and the overall 5-year survival rate has not significantly improved[1]. Local failure rates range from 50% to 80% in patients with resected and locally advanced disease[4]. Cardillo et al.[22] have demonstrated that uncontrolled locoregional disease is the leading cause of hospitalization among patients with pancreatic cancer. IORT has emerged as a safe and effective procedure that enhances local control without increasing morbidity or mortality risks[9,14,15,23]. A meta-analysis encompassing 15 studies in 834 patients has demonstrated that IORT significantly increases locoregional control and OS in patients with resectable pancreatic cancer, without increasing postoperative complication

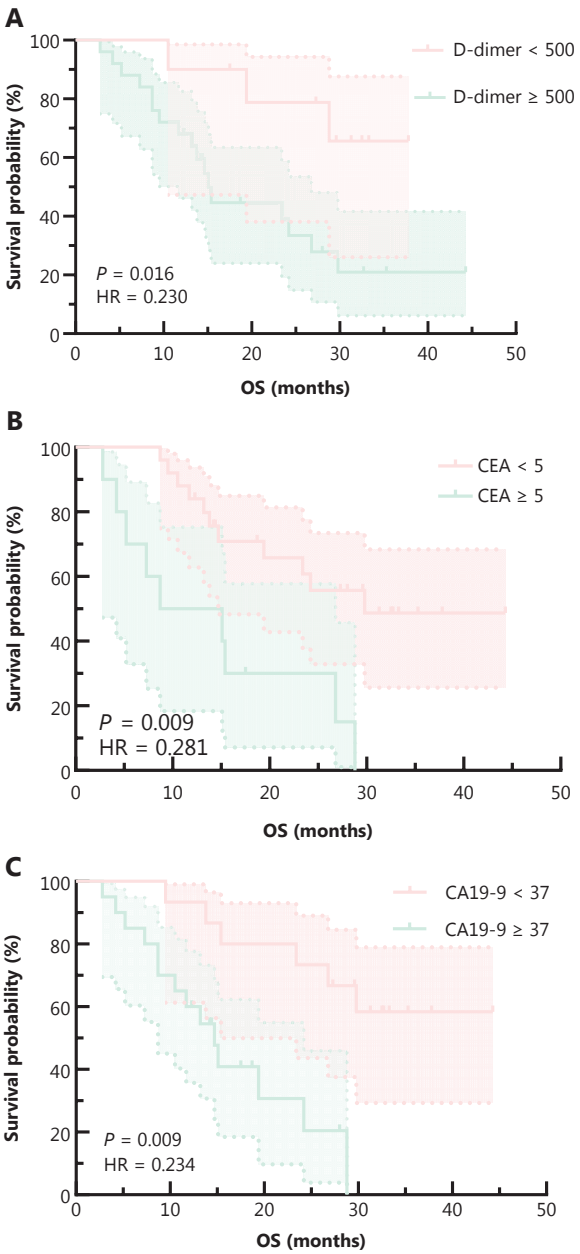

Figure 2 Kaplan-Meier survival curves showing overall survival (OS) according to D-dimer (A), CEA (B), and CA19-9 (C).

rates or operation-related mortality[15]. However, some reports have suggested that IORT might lead to severe postoperative complications without improving OS[24-27]. In our study, only 7 patients experienced locoregional recurrence. The median TTF and OS were 11.67 months and 22.2 months, respectively, thus indicating a lower locoregional recurrence rate than reported in historical data. Recruitment for this study is ongoing, and long-term follow-up data are not yet available.

Table 4 Postoperative complications

Variable	No. (%)
Pancreatic fistula	33 (94.2)
A	30 (85.7)
B	2 (5.7)
C	1 (2.9)
Delayed gastric emptying	7 (20.0)
A	3 (8.6)
B	4 (11.4)
Intra-abdominal abscess	1 (2.9)
Multiple organ failure	1 (2.9)

Because most reported experiences have come from single institutions and have involved limited numbers of patients, the true role of IORT in the clinical management of pancreatic cancer remains unclear.

Chen et al.[13], in a study of the long-term outcomes of intraoperative electron beam radiation therapy in China, observed that delayed gastric emptying was the most common postoperative complication (7.7%), with pancreatic fistula observed in 8 patients (3.2%) and biliary fistula observed in 3 patients (1.2%); moreover, gastrointestinal hemorrhage was observed in 7 patients (2.8%)[28]. In our study, pancreatic fistula was the predominant complication (grade A: 85.7%, grade B: 5.7%, grade C: 2.9%). No instances of biliary fistula and gastrointestinal hemorrhage were observed. The IORT dose was not significantly associated with postoperative complications. Our findings suggested that IORT can be safely integrated into the management of resectable pancreatic cancer, and demonstrates acceptable morbidity and mortality rates.

The identification of patients who might benefit from IORT remains a crucial area of investigation. CT imaging characteristics and serum CA19-9 levels have been proposed for stratification of patients with locally advanced pancreatic cancer undergoing IORT according to progression risk[28]. In a study by Kazuhiko et al.[29] exploring IORT with or without external beam radiotherapy for resected pancreatic cancer, factors such as chemotherapy use, degree of resection, CA19-9 level, and pathological node stage have been found to significantly influence OS. Similarly, in the current study, CA 19-9 levels, CEA levels, and D-dimer levels were identified as independent prognostic factors for OS. Patients with normal serum CA19-9 levels had a significantly longer median OS

than those with elevated CA19-9 levels (14.733 months *vs.* not available) (P = 0.009). Given the limited sample size in the current study, a nomogram for stratifying patients with resectable pancreatic cancer into low- and high-risk groups after IORT was not constructed. CEA is a widely used marker for predicting pancreatic cancer prognosis[30-33]. Sato et al.[32] have demonstrated that high serum CEA serves as an indicator of short survival after pancreaticoduodenectomy for pancreatic cancer. In agreement with previous research findings, CEA was significantly higher in individuals with shorter survival in our study. D-dimer levels, indicative of cancer-related hypercoagulation and metastatic potential, were also associated with poor survival outcomes[34]. A meta-analysis has indicated the association between higher preoperative D-dimer levels and advanced tumor stage, larger tumor size, as well as distant metastases[35]. In the present study, the median OS of patients with high and low D-dimer levels was 15.067 months and not reached, respectively (P = 0.016). Inflammation, recognized for its role in tumourigenesis and metastasis[36], has been extensively studied in pancreatic cancer. A study including patients with pancreatic cancer with liver metastases has reported that the prognostic nutritional index, the neutrophil-to-lymphocyte ratio (NLR), CA19-9, CEA, gender, and chemotherapy are significantly associated with OS[33]. Factors such as the NLR, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, neutrophil-platelet score, systemic inflammation response index, ratio of NLR to pAlb, systemic immune inflammation index, systemic inflammation score, fibrinogen-NLR score, and ratio of NLR to albumin have no prognostic value regarding OS.

A study including 30 patients with pancreatic cancer has revealed elevated levels of cytokines associated with the PI3K/SMAD pathway in peritoneal fluid after IORT[37]. Furthermore, peritoneal fluid from IORT-treated patients inhibits the growth, migration, and invasiveness of pancreatic cancer cells. These findings suggest that IORT exerts anti-tumor effects by activating immune responses. Combining IORT with novel therapeutic agents, such as immune checkpoint inhibitors, in clinical trials might be a promising strategy to enhance outcomes for patients with pancreatic cancer.

In the past, IORT has relied primarily on visual and manual guidance without the use of 3D treatment planning or correction for tissue heterogeneity. This approach has limited the precision of dose application and the accurate documentation of dose distribution within tissues. Combining intraoperative CBCT with preoperative CT scans has enabled precise dose calculations while ensuring accurate positioning of the radiation source/applicator[19]. Roeder et al.[38] have demonstrated the application of image-guided IORT in the abdominopelvic region, by incorporating real-time intraoperative dose calculations based on individual patient anatomy. However, their study focused on a single patient with locoregionally recurrent rectal cancer after neoadjuvant re-chemoradiation[38]. In our study, only 2 patients received image-guided IORT. However, future treatments will incorporate this technology more extensively.

Several study limitations must be acknowledged. First, the single-arm study design precludes definitive conclusions from being drawn regarding the potential superiority of adding IORT to surgery versus surgery alone, in terms of complications or treatment outcomes. Prospective randomized controlled trials are required. Because of the increasing numbers of laparoscopic operations, the safety of surrounding organs cannot be fully ensured, and laparoscopic intraoperative radiotherapy has not yet been performed. The slow enrollment has affected study progress and the efficiency of data collection. To ensure a scientific and effective study, the research team decided to analyze the existing data for timely evaluation of the research progress and treatment effects, to enable adjustments or decide whether to continue the study. The findings will also require validation through further follow-up, because of the limited participant cohort. Additionally, the protocol did not specify postoperative adjuvant chemotherapy.

Conclusions

In summary, our findings suggest that IORT can be safely integrated into the management of resectable pancreatic cancer, and is acceptable in terms of morbidity and mortality. Patients with lower levels of CEA, CA19-9, and D-dimer might experience prolonged survival.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xingyun Chen, Shuo Li, Chuntao Gao, Wei Wang, Rui Liu, Jihui Hao.
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Contributed data or analysis tools: Xingyun Chen, Shuo Li.
Performed the analysis: Xingyun Chen, Shuo Li.
Wrote the paper: Xingyun Chen, Shuo Li.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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